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Tick-borne diseases and autoimmunity: A comprehensive review

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ABSTRACT

Tick-borne diseases (TBDs) are emerging and reemerging diseases transmitted by ticks, which portray wide heterogeneity and global distribution. TBDs may present acute clinical pictures that resemble those of autoimmune diseases (i.e., musculoskeletal symptoms, cutaneous involvement, neurologic impairment, renal failure, etc.), and in some cases infection is considered a triggering factor for autoimmunity (e.g., rheumatoid arthritis, autoimmune thyroid disease, vasculitides). The clinician should consider TBDs among the differential diagnoses when approaching autoimmune-like signs in areas of tick infestation. Epidemiological setting (e.g., endemic areas, seasons) and an accurate diagnostic approach (i.e., clinical history, physical examination and laboratory tests) are necessary to confirm TBDs. Further, control and prevention of TBDs is warranted. Research in the fields of ticks microbiome and vaccination (i.e., wildlife and humans) are ahead to control vector transmission and bacterial infection. This review offers a comprehensive update on TBDs and their relationship with autoimmunity.

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Abbreviations

TBD	Tick-borne disease
TBDs	Tick-borne diseases
ADs	Autoimmune diseases
RA	Rheumatoid arthritis
GBS	Guillain-Barré syndrome
CNS	Central nervous system
LD	Lyme disease
RF	Relapsing fever
US	United States
BBB	Blood-brain barrier
STARI	Southern-tick-associated rash illness
SSc	Systemic sclerosis
AS	ankylosing spondylitis
GCA	Giant-cell arteritis
MS	Multiple sclerosis
GBS	Guillain-Barré syndrome
TM	Transverse myelitis
HT	Hashimoto thyroiditis
APS	Antiphospholipid syndrome
GPA	Granulomatosis with polyangiitis
PBS	Primary biliary sclerosis
SLE	Systemic lupus erythematosus
PMR	Polymyalgia rheumatica
AITD	Autoimmune thyroid disease
BD	Behçet's disease
TNF	Tumor nuclear factor
Osp	Outer surface protein
aPL	Antiphospholipid antibodies
TLR	Toll-like receptor
PNS	Peripheral nervous system
LFA	Lymphocyte function-associated antigen
EC	Endothelial cells
RMSF	Rocky mountain spotted fever
TSH	Thyroid-stimulating hormone
GD	Grave's disease
aCL	Anti-cardiolipin
Anti-β2GP1	anti-β2-glycoprotein-1
LAC	Lupus anticoagulant
ANCA	Anti-neutrophil cytoplasmic antibody
TA	Thromboangiitis obliterans
HME	Human monocytic ehrlichiosis
HGA	Human granulocytic anaplasmosis
AHA	Autoimmune hemolytic anemia
IT	Immune thrombocytopenia
Th1	T-helper cell type 1
TBEV	Tick-borne encephalitis virus
ADEM	Acute disseminated encephalomyelitis
ASMA	Anti-Smooth-Muscle Antibody
AMA	Antimitochondrial antibodies
HFVs	Hemorrhagic fever viruses

1. Introduction

Tick-borne diseases (TBDs) are emerging and re-emerging pathogens [1]. Recently, several emerging infections such as Zika and Chikungunya viruses have been associated with autoimmune phenomena [2,3]. TBDs may present acute clinical pictures that resemble those of autoimmune diseases (ADs) (i.e., musculoskeletal symptoms, vasculitis, cutaneous involvement, neurologic impairment, renal failure, etc.) [4,5]. Further, the association of some ADs with TBDs (i.e., rheumatoid arthritis [RA], Guillain-Barré syndrome [GBS]) have increased the suspicion of induced autoimmunity through mechanisms of bystander activation, epitope spreading, molecular mimicry and original antigenic sin [6–8]. In addition, apoptosis induced by bacteria promoting self-peptides

presentation by antigen-presenting cells have also been demonstrated to trigger autoimmunity, likely due to enhanced Th17 responses [9].

TBDs are a unique human model to study the relationship between infections and ADs [10]. Molecular mimicry appears to be the main mechanism associated with TBDs and autoimmunity [11]. As emerging/re-emerging pathogens with a worldwide distribution, the clinician should consider TBDs in the differential diagnosis when approaching autoimmune-like signs in areas of tick infestation. Herein, the association between TBDs and autoimmunity is reviewed together with the possible autoimmune mechanisms explaining this association.

2. Ticks

Ticks are obligate bloodsucking ectoparasitic arthropods that feed from birds, mammals, reptiles and amphibians [12]. They are mainly located in tropic and subarctic areas and factors such as temperature and humidity play a key role in their growth and development [13]. Climate change and landscape modifications by humans have favored ticks spread and have increased the incidence of TBDs [12,14]. Ticks are classified in four families, namely *Ixodidae* (hard-bodied), *Argasidae* (soft-bodied), *Nuttalliellidae* and *Laelaptidae* [13]. Hard-bodied ticks (*Ixodidae*) are the most common vector for TBDs in the United States (US). Only 28 species out of 878 from these families have been recognized to transmit human pathogens, which include organisms such as viruses, protozoa and bacteria (Table 1) [13]. Morphology, taxonomy and geographic distribution maps of ticks have been reviewed elsewhere [13,15,16].

Ticks undergo a two year, three-stage life cycle: larva, nymph and adult [4,17]. Hard ticks need to feed once in each stage, whereas soft ticks feed multiple times in a lifetime [12]. Larva grow over winter and emerge the following spring at nymphal stage [4,5]. Ticks can acquire pathogens at any stage of their cycle (e.g., from reservoir, such as white footed mice, squirrels and birds), but nymphs are most prone to transmit infections, with a peak in spring and summer months [4,18]. Generally, hard-bodied ticks must feed for 48 to 72 h or longer to infect humans, whereas less than 24 h seems to be enough to transfer microorganisms in soft-bodied ticks [18]. Diseases produced by these microorganisms are summarized in Table 1.

Since heterogeneity in morphology, taxonomy and geographic distribution have been shown, research in the fields of ticks' microbiome and vaccination (i.e., wildlife animals and humans) are ahead to control vector transmission and bacterial infection [12,19–21].

3. Infectious diseases and ticks

3.1. Bacteria

3.1.1. Borrelioses

Borrelioses are infectious diseases produced by *Borrelia* spp. and characterized by heart, central nervous system (CNS), joints and skin involvement. They are transmitted by ticks and produce three main diseases: Lyme disease (LD), relapsing fever (RF) and Southern Tick-Associated Rash Illness (STARI) (Table 1) [22].

3.1.1.1. Epidemiology. The three conditions produced by *Borrelia* spp., namely LD, RF and STARI [23], have been widely described across the globe affecting thousands of people every year (Table 1) [18,24–32]. However, accurate prevalence is unknown because of misdiagnoses and underreported cases [4]. Interestingly, some countries have reported a high seroprevalence of *Borrelia* spp. in both healthy individuals and in those with ADs [33–37]. Physicians should consider borrelioses as a differential diagnosis of ADs and its possible role as a trigger for ADs [38–40]. However, as emphasized below, a diagnosis of borrelia-associated disease, much like Lyme, should be based on rigorous criteria to avoid misdiagnosis and inappropriate therapy.

3.1.1.2. Pathophysiology. Molecular mimicry and exaggerate immune responses are two of the mechanisms suggested to explain the association between ADs and *Borrelia* spp. infection (Table 2). The pathogenesis, including host immune responses, has been extensively described elsewhere [41].

3.1.1.2.1. Skin inflammatory response. Up to 80% of patients develop a skin lesion at the site of inoculation within 30 days after a tick bite, which is known as erythema migrans or “bull's-eye” rash [4,41]. After the spirochete is inoculated in the skin and the innate immune response takes place, monocytes and dendritic cells produce large amounts of Type I Interferon (IFNs, i.e., IFN-α and IFN-β) and Interleukin (IL)-10 [41,42]. In addition, high levels of TNF-α, IL-1β, and IL-6 have been found in erythema migrans lesions, particularly in patients with systemic symptoms of LD (i.e., neuroborreliosis) [42]. Interestingly, patients infected with *B. burgdorferi* present a faster spreading of erythema migrans and disclose systemic symptoms more frequently than patients with *B. afzelii* infection, suggesting that different responses occur among different *Borrelia* spp. species [41].

3.1.1.2.2. Joint inflammatory responses. Most patients with infection by *Borrelia* spp. develop acute events of arthralgia and arthritis, particularly by *B. burgdorferi* infection. Sixty percent of

Table 1
Tick-borne diseases. Geographical distribution, proposed autoimmune mechanisms and related autoimmune diseases.

Tick	Bacteria species	Tick-borne disease	Geographical distribution	Ref.
A. americanum	*B. lonestari, R. rickettsi,*	STARI	North America	[233]
	E. chafeensis	RMSF	Middle East	
		Human monocytic ehrlichiosis		
Ornithodoros spp.	*B recurrentis, B hermsii,*	Relapsing fever	North Africa and middle east.	[233]
	B duttoni, B latyschewii,			
	B turicatae, B. conori			
I. ricinus	*B. burgdorferi, B. garinii,*	Lyme disease	North America, Europe, Middle East, Asia and Africa.	[233,380,114,381]
I. scapularis	*B. afzelii, B. miyamotoi,*	Non-eruptive rickettsiosis		
I. pacificus	*B. bavariensis, R. helvetica*	Human granulocytic anaplasmosis		
I. persulcatus	*Anaplasma* spp.,	Babesiosis		
I. dentatus	*B. divergens,*			
	B. microti MO-1			
	WA-1, CA-1, CA-2, KO1, TBEV			
R. sanguineus	*R. conorii*	Mediterranean spotted fever	Europe, Africa, Middle East	[233]
R. pumilio		Israel spotted fever		

STARI: Southern Tick-Associated Rash Illness, RMSF: rocky mountain spotted fever, TBEV: tick borne encephalitis virus.

Table 2
Autoimmune mechanisms induced by Tick-borne infection.

Microorganism	Factors	Components	Propose mechanism	Effect	Ref.
B. burgdorferi	*Skin*	Macrophages and dendritic cells.	Activation of TLR-2	Production of TNF (α, β),IL-1β, IL-6, IL-8, E-selectin, VCAM1 and ICAM 1	[41,42]
	Joints	*Borrelia* spp. nucleic acids release	TLR-2 and TLR-8 activation by joint macrophages and dendritic cells	Chronic production of Type I IFNs, TNF-α IL-6, IL-8 and IL-17	[43–49]
		Borrelia spp. surface molecules	Molecular mimicry with ApoB-100 (synovial protein)	Induce autoimmune response	
		HLA-DRB1*0401 or HLA-DRB1*0101	OspA proteins presented through MHC II	Induce autoimmune response	
		Activated by cytokine environment	Increase production of IL-1β	Joint chronic destruction and inflammation.	
	CNS/PNS	OspA and flagellar proteins.	Cross reactivity with integrin LFA-1, Schwann cells and activation of $CD8^+$ T-cells	Chronic CNS/PNS immune-mediated inflammation	[50–52]
	Heart	*Borrelia* spp. infiltration	Enhance local inflammatory response	Induce chronic carditis and possibly produce heart conductance system impairment	[53,54]
		OspA	Molecular mimicry with cardiac myosin	Induce autoimmunity against myosin	
	Liver	Borrelia flagellin	Molecular mimicry with pyruvate dehydrogenase complex E2 subunit	Induce production of anti-mitochondrial antibodies	[277]
	Thyroid	Borrelia epitopes	Molecular mimicry with TSH receptor, TGO and TPO	Thyroid disease	[255]
Rickettsia spp.	Joint	Humoral response/Arthritogenic peptides in *Rickettsia* spp.	Immune-complexes formation	Reactive arthritis: Immune-complexes deposition	[68]
	Vascular	Endothelial cells/Immune response	ECs destruction and release of self-antigens/Local inflammation due to *Rickettsia* spp. within ECs	aPLs production/Thromboangiitis obliterans	[66]
	Thyroid	Bacterial epitopes and genetic: HLA predisposition	Molecular mimicry: homology between rickettsial epitopes and self-antigens (i.e., TSH receptor/soluble liver antigen/liver-pancreas proteins), with specific binding motifs to HLA DRB1*0301 (*in silico* models)	Thyroid disease	[67]
	Liver			Liver disease	[70]
C. burnetti	Liver	β-subunit of bacterial RNA polymerase	Possible molecular mimicry	Induce production of anti-mitochondrial antibodies	[280]
B. microti	Hematologic	Erythrocytes and humoral response	immune-complex deposition	Hemolysis	[216]
Tick-borne encephalitis virus	Brain	Myelin	Molecular mimicry, bystander activation and epitope spreading	Demyelinating and neurodegenerative lesions	[224]

CNS: central nervous system, PNS: peripheral nervous system, TLR: toll-like receptor, OspA: outer surface protein type-A, LFA-1: lymphocyte function-associated antigen-1, aPL: antiphospholipid antibodies.

untreated patients in the US develop chronic and intermittent attacks of joint swelling and pain, primarily in large joints [18]. *Borrelia* spp. migrates through blood stream to joints. Toll-like receptor (TLR)-8 is activated due to spirochetal nucleic acids release. Interestingly, a cooperative TLR-2 and TLR-8 signaling activates the production of Type I IFNs, Tumor necrosis factor (TNF)-α, IL-6 and IL-8 [43]. Further, chronic production of IL-1β and IL-17 by *Borrelia* spp. infection has been recognized [44,45]. These mechanisms are considered to account for chronic arthritis in patients with LD.

Patients with LD arthritis frequently disclose the HLA-DRB1*0401 or HLA-DRB1*0101 alleles, which are often observed in RA patients (Table 2). Interestingly, chronic LD arthritis is characterized by high titers of IgG antibodies against outer surface protein type A (OspA), the first surface protein identified in this bacterium, suggesting the existence of molecular mimicry between OspA and molecules presented by the major histocompatibility complex class II [46–48].

B. burgdorferi peptides portray similarities with human ApoB-100 complexes. Patients with treatment-resistant LD arthritis disclose high levels of ApoB-100 in their joints. It is theorized that autoreactive T and B cell against ApoB-100, due to molecular mimicry, contribute to autoimmunity in chronic LD arthritis [49].

3.1.1.2.3. Neurologic inflammatory responses. About 15% of patients with LD develop CNS and peripheral nervous system (PNS) impairment. The most common presentations include facial palsy, transverse myelitis (TM) and multiple sclerosis (MS)-like symptoms [18]. *B. garinii* infection appears to be associated with a higher accrual of neurological manifestations [4]. Persistent activation of $CD8^+$ and molecular mimicry during *Borrellia* spp. infection play a pivotal role in autoimmunity development. OspA may trigger chronic inflammation in the CNS through molecular mimicry with the integrin Lymphocyte Function-associated Antigen-1 (LFA-1). Further, *B. burgdorferi* -flagellar protein shares a similar structure with Schwann cells components, which could induce the production autoantibodies to myelin basic protein during infection, injuring the PNS [50–52].

3.1.1.2.4. Cardiac inflammatory responses. Cardiac involvement in LD presents a wide spectrum, ranging from asymptomatic to severe manifestations [53]. Both myocardial infiltration by *Borrelia* spp. and molecular mimicry between OspA and myosin have been proposed as the main mechanisms of damage. On the other hand, immune mediated cardiac conductance impairment (e.g., atrioventricular block) has not been observed [53,54].

3.1.1.3. Clinical features. Mainly produced by *B. burgdorferi,* LD presents three stages: 1) early localized disease; 2) early disseminated disease; and 3) late disseminated disease. The first stage begins within 30 days after tick bite, and typically presents with a painless skin rash known as erythema migrans, which usually remits after treatment. After a month, early and late disseminated phases develop, and debut with clinical symptoms mimicking ADs, such as RA, systemic sclerosis (SSc), and MS [4,18,42,55,56].

In contrast, RF produced by *B. recurrentis* classically begins within 14 days after tick bite. The first febrile episode lasts about 3 days, and is followed by 7-days fever-free interval. Neurological involvement including meningismus, myelitis and facial palsy, is common [5]. On the other hand, patients with STARI are mainly observed in non-endemic areas of LD, disclose a similar rash pattern (i.e., erythema migrans) but with a smaller diameter, and without fever. Initial symptoms include mild myalgia, arthralgia and neck stiffness, less severe than in LD. Chronic symptoms are infrequent and its lack of severity makes it easy to manage [57,58].

3.1.1.4. Diagnosis and treatment. Spirochaetes diagnosis has always been challenging. Diagnostic tests based on the search of antigens or DNA of *Borreliae* spp., such as polymerase chain reaction (PCR), have not shown enough accuracy [4]. The Centers for Disease Control and Prevention recommend the use of a 2 step procedure to diagnose LD: first, a sensitive screening test, such as enzyme linked immunosorbent assay (ELISA) must be performed and, if the result is positive or equivocal, a western blot must be performed to confirm results; most authorities require the presence of antibodies against at least 2 (IgM) or 5 (IgG) specific *B. burgdorferi* proteins. All LD diagnosis need to have a clinical suspect for an accurate diagnosis [4]. RF and STARI diagnosis is tough due to the lack of specific serological assays to specific borrelia antigens. Therefore, clinical diagnosis and epidemiological setting are the most appropriate approaches [5].

Treatment for borreliosis is well tolerated and has high rates of success and complete remission of symptoms. It is recommended to treat patients with oral doxycycline 100 mg twice a day for 10 to 14 days. This regimen includes LD patients with neurological, cardiac and articular manifestations in the early disseminated onset of disease [4]. Some evidence suggest that monotherapy with antibiotics in the late disseminated phase is not enough and nonsteroidal antiinflammatory drugs should be administrated for symptomatic relief. Meningitis secondary to LD must be treated with intravenous ceftriaxone 2 g once a day, although oral doxycycline has shown to be as effective as intravenous ceftriaxone [4,59]. Patients with RF and STARI infection should be treated with tetracycline 500 mg three to four times a day for five to ten days; doxycycline can also be used [5].

3.1.2. Rickettsioses

3.1.2.1. Epidemiology. Rickettsioses are emerging/reemerging zoonotic infections produced by gram-negative bacteria, which present a worldwide distribution (Table 1) [60]. More than 30 species and subspecies have been identified and have been linked to human disease. Their transmission depends on the geographical distribution of their vectors such as lice, mites and fleas [61]. Their vectors act as reservoirs, but small mammals (i.e., dogs, wild animals) can act as secondary reservoirs or amplifiers. Humans are considered accidental hosts [60–63]. Herein, only tick-borne rickettsioses (e.g., rocky mountain spotted fever, Mediterranean spotted fever) will be covered.

3.1.2.2. Pathophysiology. Endothelial cells (EC) stand out as the main target of invasion of tick-borne rickettsioses, particularly those on the lining of small and medium-sized blood vessels. The main characteristics of rickettsial diseases are vascular inflammation, damage to blood vessels and altered vascular permeability, a triad known as "*Rickettsial vasculitis*". Several features are observed during rickettsial infection, which ultimately lead to phagosome evasion, endothelial cell injury (i.e., vasculitis) and bacteria spreading. This mechanisms have been thoroughly reviewed elsewhere [64,65].

Regarding autoimmune phenomena, data are scarce. For instance, a study found up to 70% of seropositivity for antiphospholipid and 50% for anti-endothelial autoantibodies in patients with Rocky Mountain Spotted Fever (RMSF). The authors considered that ECs damage and the release of self-antigens may account for these phenomena [66]. Further, an Australian study demonstrated the existence of homology between rickettsial proteins and TSH receptor, as well as common binding motifs to HLA DRB1*0301, in a patient with Grave's disease (GD) associated with rickettsial infection [67]. Additionally, reactive arthritis is uncommon among rickettsioses symptoms, although some cases have been reported (see below). Both immune-complexes deposition [68] and potential molecular mimicry in selected strains [69] have been proposed. Recently, Paiardini et al. [70] found similarity between autoimmune hepatitis target-antigens (i.e., soluble liver antigen/liver-pancreas protein) and *R. prowazekii* surface antigens (i.e., PS120) (Table 2). Further, binding mode and affinity to HLA DRB1*0301 was assessed, yielding compelling similarities. Noteworthy, we did not find any case of autoimmune hepatitis and tick-borne rickettsial disease association.

3.1.2.3. Clinical features. The classic triad is described as 1) febrile illness, 2) headache and 3) exanthema. Some infections present an inoculation eschar (i.e., '*tache noire*') and lymphadenopathies. Nonetheless, rickettsioses may present without rash [63]. Thrombocytopenia, neutropenia and elevated liver enzymes are common. Severity level may be variable among infecting species. For instance, *R. rickettsii* infection, which provokes RMSF, usually presents a more severe compromise than other tick-borne rickettsioses [71]. Affected blood vessels lining is often localized in vital organs. This noxious effects on endothelia lead in severe cases to neurological symptoms (seizures, coma, delirium), pulmonary symptoms (edema, respiratory distress syndrome), acute renal failure (due to hypovolemic hypotension), and, lastly, multisystem organ failure. Although vascular lining is utterly affected, disseminated intravascular coagulation is seldom seen [64].

3.1.2.4. Diagnosis and treatment. Clinician suspicion is pivotal and should drive diagnostic workup. ADs stand out as some of the most common differential diagnoses (e.g., systemic vasculitides). An adequate diagnostic approach should include tick exposure, recreational/occupational exposure to tick-infested areas, travel to areas where tick-borne rickettsial diseases are endemic, occurrence of similar illness in family members or coworkers [63]. The absence of one or more of these factors does not exclude a possible TBD, and unrecognized tick bites are common [72].

Although positive culture remains the gold standard for diagnosis, this technique is difficult to yield positive results. Swab samples from vesicles or eschars are the most adequate. Skin biopsy may work as well. Serological assays, which measure antibodies, are the most widely used method, particularly immunofluorescence. However, drawbacks have been identified: it may yield cross-reactions among species and is not sensitive during the first days of illness. To establish a diagnosis, two separate samples (i.e., two weeks apart) must be taken, during acute and convalescent phases. An accurate diagnosis will be established if seroconversion (>= 4-fold increase in titer) is observed. Although both IgM and IgG may be used, the former may disclose false-positive results. To increase specificity, Western-blot or cross-absorbtion may be performed [61,63].

Molecular tools are available in several laboratories, and may assist routine diagnosis in selected facilities. Amplification of several preserved genes using PCR or quantitative PCR are commonly used. They yield fast and reliable (i.e., specific and sensitive) diagnosis on a myriad of samples (e.g., eschar swab, biopsy, blood, serum, removed tick, etc) [61]. Regarding treatment,

doxicicline, the main treatment agent, should not be delayed, due to the potential life threat [61,63]. Doxicicline stands as the standard therapy in both pediatric and adult populations. Short courses may be given with adequate effectiveness [63].

3.1.3. Ehrlichiosis and anaplasmosis

3.1.3.1. Epidemiology. Two major syndromes are associated with these gram-negative microorganisms, namely human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA). HME and HGA are emerging TBDs, produced by *E. chafeensis* and *Anaplasma* spp. respectively. Noteworthy, Ehrlichia genus comprises other species (i.e., *E. ewingii, E. canis, E. ruminatum, E. mineirensis, E. muris*-like) which have been recently found to produce disease in humans [73]. HME cases have been mainly reported in the US, although Ehrlichioses have been observed in Asia, Africa and South America [74,75]. On the other hand, HGA has been observed in Europe, Asia (i.e., China, Japan, South Korea) and the US [76]; seropositivity in several countries with identified transmission exceed 10%, which suggest that asymptomatic or mild auto-resolutive cases may be present. Up to 36% of patients may present co-infections with *B. burgdorferi* or *Babesia microtii,* probably due to a shared vector (i.e., *Ixodes*) (Table 1) [77].

3.1.3.2. Pathophysiology. Each genus presents a particular tropism. *Ehrlichia* spp. infect monocytes and macrophages (i.e., mononuclear phagocytes), contrasting *Anaplasma* spp., which infect mainly neutrophils. Both microorganisms undergo evasion of host defense mechanisms and replicated inside target cells. *Anaplasma* spp. infection exhibits a marked neutrophil recruitment to the infected area, which amplifies the inflammatory response. This may explain the striking tissue destruction that appears to be independent of bacteria quantity and secondary to host response. Interestingly, *Anaplasma* spp. seem to induce immunosuppression, as most of the fatal cases are due to opportunistic infections. Infection mechanisms have been reviewed elsewhere [73]. Autoimmune phenomena appear to be rare, as few reports are available (see below); no mechanisms have been proposed.

3.1.3.3. Clinical features. Usually, HME and HGA present with unspecific flu-like symptoms, such as fever, myalgia, arthralgia and headaches. Maculopapular or petechial rash is frequent in children with HME, but is observed in up to 20% of adults; it usually spares palms and soles. Neurologic symptoms, such as coma and seizures may be seen in a fifth of patients. Noteworthy, HME tends to be more severe than HGA, and may present with multi-organ failure and toxic septic shock syndrome. Aseptic meningitis, adult distress respiratory syndrome or hepatic failure may be observed. Immunocompromised hosts (e.g., HIV, post-transplantation, corticosteroid use, elderly) usually present more severe symptoms. The high incidence in elderly suggests immunosenescence as an important factor for illness. Thrombocytopenia and leukopenia (i.e., lymphopenia or neutropenia) are usually seen, accompanied by liver enzyme elevation. Further, HGA presents similar flu-like symptoms, however rash is seen in less than 10% of patients. Although central nervous system involvement is seldom observed, peripheral nervous system manifestations have been reported.

3.1.3.4. Diagnosis and treatment. Diagnosis is made based on clinician suspicion: any patient with fever, leukopenia, thrombocytopenia, increase liver enzymes and a recent tick bite between May and July, should be ruled out of ehrlichiosis. Culture has been recognized as the gold standard for definitive diagnosis, but is extremely difficult to obtain. Molecular tests, such as PCR, yield a high sensitivity in blood and cerebrospinal fluid samples during active infection, and before detection of antibody. The principal diagnostic criteria remain serologic, by using indirect immunofluorescence in *E. chafeensis* infected cells. We must obtain a basal sample and a convalescent sample, and a 4-fold increase compared to either baseline or a decrease in antibodies titers, with a minimum of 64. After 4 weeks, most patients present a positive serologic test. A number of differential diagnosis are probable, due to unspecific symptoms. Infectious diseases should be rule-out, although ADs remain as possible confounders [74]. Rapid treatment with doxycycline 100 mg twice per day for 5 to10 days is warranted, in order to reduce morbi-mortality [74].

3.1.4. Q fever

3.1.4.1. Epidemiology. Q fever is a zoonotic infection caused by *Coxiella burnetii*, a gram-negative intracellular spore bacterium. This disease presents a worldwide distribution and extensive reservoirs in domestic and wild animals. Although spores inhalation of contaminated aerosols are the main spread mechanism, tick bites have been proven to transmit the disease [78].

3.1.4.2. Pathophysiology. Immune response against bacteria is often T-cell dependent, however, it does not always lead to *C. burnetii* eradication [79]. In vertebrate hosts, *C. burnetii* infection results in the formation of granulomas in infected organs, due to the migration of monocytes through the vascular endothelium [80]. Furthermore, specific immunoglobulins are secreted following infection. IgG is mainly directed against phase II antigen, whereas IgM is directed against both phase I and II cells [7]. On the other hand, it has been observed an important role of TLR-4 in granuloma formation, since knock-out mice for this receptor develop less granulomas [79]. Additionally, TLR-4 modulates the cytokine response, mainly IFNγ and TNFα, following acute infections [79]. During chronic Q fever the immune response is ineffective, and may also be harmful, causing leukocytoclastic vasculitis and glomerulonephritis [81].

3.1.4.3. Clinical features. Most of patients are asymptomatic. However, symptomatic patients can course with acute or chronic disease. Regarding acute illness, patients usually present flu-like disease with varying degrees of pneumonia and hepatitis [82]. The mortality rate ups to 2%, being myocarditis the main cause [83].

Chronic illness may occur months or years after acute illness [84]. Pregnancy, immunosuppression, heart valve lesions, and vascular abnormalities, pose patients at high-risk [85]. Other forms of chronic infection are protracted fever, chronic fatigue syndrome, osteo-articular infection, infection of vascular grafts and granulomatous hepatitis [85].

3.1.4.4. Diagnosis and treatment. Laboratory findings are usually unspecific and diagnosis is typically made by serology [86]. The most common used serologic technique is the micro-immunofluorescence test [87]. After positive serology, patients are tested for the presence of anti-phase I and anti-phase II IgG, IgM, and IgA antibodies. Seroconversion to these antibodies usually occurs 7 to 15 days after the onset of disease. An IgG titer greater than 800 against phase I antigens is usually associated with chronic infection whereas a titer of 200 for IgG and 50 for IgM against phase II antigens is suggestive of a recent Q fever infection [88]. Since development of chronic infection is common, serology must be retested 6 months after the onset of disease. Further, other laboratory data such as leukocytosis, anemia, increase of erythrocyte sedimentation rate and liver enzymes could be found [86,89]. Detections of *C. burnetti* by DNA amplification (i.e., PCR) are usually performed in histopathology studies (e.g., cardiac valve samples) [89,90]. Q fever usually resolves spontaneously after 2 weeks of onset. However, pharmacologic treatment is warranted in

symptomatic patients. Treatment with tetracycline and doxycycline is recommended. Fluoroquinolones (e.g., ofloxacin, pefloxacin) have also been effective [86].

3.1.5. Tularemia

3.1.5.1. Epidemiology. Tularemia is caused by the gram-negative coccobacilli *Francisella tularensis*, which presents a worldwide distribution. Tularemia cases are more frequent across the northern hemisphere. Transmission may be due to contact with contaminated animal products, water, aerosolized particles or by arthropods, including ticks [91]. A French registry reported that up to 20% of cases were associated with tick bites [92].

3.1.5.2. Pathophysiology. As an obligate intracellular bacterium, *F. tularensis* evades the phagosome and initiate its replication within host cells, ultimately leading to cell death and bacterial release. It may infect a variety of cells including macrophages, neutrophil, dendritic cells, ECs, hepatocytes and type II alveolar cells. The effective replication process displayed by *F. tularensis* accounts, at least partly, for its high virulence. These mechanisms have been reviewed elsewhere [93].

3.1.5.3. Clinical features. Two main groups of clinical symptoms are identified, namely ulceroglandular and typhoidal. The former is the most frequently described (i.e., 75% of cases) and usually presents mucocutaneous involvement and lymphoadenopathies. On the other hand, typhoidal is characterized by high fever, hepatosplenomegaly and pneumonia [91].

Rare cases of *F. tularensis* infection-associated erythema nodosum [92,94], posterior uveitis [95] and aortitis [96] are available in the literature. Although they were not diagnosed as ADs, they illustrate tularemia should be ruled out when these entities are observed before an autoimmune etiology is diagnosed.

3.1.5.4. Diagnosis and treatment. Serology is the most frequently ordered diagnostic test for *F. tularensis* infection. When microagglutination studies are obtained, titers equal to or more than 1:128 are considered positive, whereas tube agglutination studies are diagnostic with titers equal to or more than 1:160. However, detectable antibodies may persist for many years after a bout of tularemia, making clinical suspicion truly important at the time of diagnosis [91]. Further, cross-reactive antibodies with *Brucella* species, *Legionella* species, *Yersinia* and *Proteus* hinder the diagnosis. Other techniques such as culture and PCR are useful [97]. *F. tularensis* should only be cultured at biosafety level 3 laboratories and appropriate protective measures should be taken when handling samples due to laboratory-acquired infections [97]. Treatment with aminoglycosides, such as streptomycin or gentamicin, are first-line therapy. In severe cases, therapy for 10 days or more, is recommended. Therapy of clinical relapses with either tetracyclines or chloramphenicol has proven to be beneficial [91].

3.2. Parasites

3.2.1. Babesiosis

Babesiosis is an anthropo-zoonotic TBD caused by *Babesia* (also called *Piroplasma*), an intraerythrocytic protozoan parasite [98]. Babesiosis shows a worldwide distribution and affects a wide variety of mammalian species, and occasionally the human [99].

3.2.1.1. Epidemiology. Human babesiosis has been reported in Latin America, Asia, Australia and Africa [100,101]. Autoimmune hemolytic anemia (AHA) and immune thrombocytopenia (IT) have been associated with *Babesia* spp. infection, although have been only reported in the US (Table 1) [11,102–107]. This suggests that AHA and AT may be either underreported or misdiagnosed in countries with high prevalence of babesiosis. Physicians of endemic areas must be aware of babesiosis and its association with ADs.

3.2.1.2. Pathophysiology. The pathogenesis of babesiosis is closely linked to the host, in which humoral and cell-mediated immune responses are crucial. The intraerythrocytic nature of parasite promotes innate and adaptive immune responses [98]. In murine models of *B. microti* and *B. duncani* infection, a shift to T helper cell type 1 (Th1) response due to IFNγ production has been observed, which leads to an enhanced production of TNFα and IL-12, and B cell stimulation, in an attempt to eliminate the intracellular pathogen [108,109]. Humoral response has been recognized as the main immunity source to remove intraerythrocytic infiltration [110–112]. However, the mechanisms by which *Babesia* spp. trigger autoimmune process remain to be elucidated.

3.2.1.3. Clinical features. Patients with babesiosis may present with asymptomatic infection. Patients with a mild to moderate illness, manifest a gradual onset of malaise and fatigue, followed by intermittent fever associated with chills, sweats, headache, arthralgia, myalgia, anorexia, and cough, which usually last for several weeks [113]. However, sometimes a fatal course may be observed [114,115]. Severe disease is most common in patients with HIV coinfection [116], malignancy [111], immunosuppression [111], splenectomy and older than 50 years old [117,118].

3.2.1.4. Diagnosis and treatment. The diagnosis of babesiosis is based on epidemiologic and medical history, physical examination, and laboratory workup. A definitive diagnosis is generally made by microscopical identification of *Babesia* spp. on thin blood smears with Giemsa or Wright staining [119].

Babesia are distinguished from plasmodia by the absence of hemozoin deposit in the ring form, the lack of banana-shaped gametocytes, and the presence of tetrads (i.e., Maltese cross) [115]. Real-time PCR is a more sensitive diagnostic test than blood smear and provides a molecular characterization of the *Babesia* species [120]. Serology is useful for supporting or confirming the diagnosis. A four-fold rise in babesia IgG titer confirms recent infection, whereas a single positive antibody titer is not confirmatory because it cannot distinguish recent from previous infection [98].

Treatment of babesiosis depends on the severity of the disease. In patients with an asymptomatic infection for longer than 3 months, (i.e., positive blood smear or PCR, but absence of symptoms), atovaquone plus azithromycin for one week is the treatment of choice [121]. On the other hand, patients with positive serology and negative blood smears and PCR should not be treated [98]. In cases of mild to moderate disease the adequate treatment consist in atovaquone plus azithromycin for 7 to 10 days [121]. Finally, in severe disease, which develops frequently in patients who have age greater than 50 years, splenectomy, malignancy, HIV infection, or immunosuppressive therapy, clindamycin plus quinine is the treatment of choice [121].

3.3. Viruses

3.3.1. Tick-borne encephalitis virus

3.3.1.1. Epidemiology. Tick-borne encephalitis (TBE) is caused by the tick-borne encephalitis virus (TBEV), a member of the family *Flaviviridae*, and is transmitted by *Ixodes* spp. ticks (Table 1) [122]. Tick-borne flaviviruses are divided in mammalian and seabird groups. TBEV belongs to the former group. Among TBEV, three subtypes are defined, namely 1) European; 2) Siberian, mainly found in Russia; and 3) Far Eastern, present in eastern Russia, China and Japan [123,124]. Further, the Mammalian group includes

Louping ill virus, which has been detected in the USA; Langat virus, described in Malaysia, and Powassan virus. The latter has been reported in Canada, northern US and eastern Russia [24,122].

3.3.1.2. Pathophysiology. The pathogenesis of TBE involve mainly the CNS [125]. Virus replication is first detected in draining lymph nodes, which is followed by viremia. During the secondary viremic phase, the virus crosses the blood-brain barrier (BBB) and enters the brain [126]. Major hallmarks of TBEV pathogenesis are neuroinflammation, followed by neuronal death, and disruption of the BBB [126,127]. In animal models, it was demonstrated that BBB integrity is compromised in TBEV-infected mice. The permeability of the BBB increases at later stages of TBEV infection, when high virus load is already present in the brain [126].

Additionally, BBB breakdown can represent as a consequence, rather than a prerequisite for CNS TBEV infection [128]. BBB is most likely involved by the activity of pro-inflammatory mediators, such as cytokines, chemokines, and matrix metalloproteinases (i.e., MMP-9), expressed in infected brain tissue [129]. Recent studies indicate that human brain microvascular ECs may support TBEV entry into the brain, via a transcellular pathway, but without altering the BBB integrity [128].

3.3.1.3. Clinical features. It is estimated that one-third of patients develop symptomatic disease after an infection with TBEV [130]. Up to 30% of cases present encephalitis, mainly caused by European TBEV, which is characterized by a two-phase disease: the first one discloses fever, whereas the second portrays neurological symptoms (i.e., meningitis in up to 50% cases, meningoencephalitis in 40%, meningoencephalomyelitis in about 10%) [131]. In contrast, Far Eastern TBV infection is usually milder, without sequelae, and a case fatality rate as low as 2% [132]. CNS injury could be fatal particularly in elderly people [132].

3.3.1.4. Diagnosis and treatment. During the first phase of illness, neutropenia, thrombocytopenia, and abnormal liver enzymes are observed. Examination of the full blood cell count reveals a raised WBC count in about 75%, elevation of C-reactive protein in more than 80% of patients, and elevation of the sedimentation rate in more than 90% of patients [133]. The available ELISA are not specific for TBEV due to cross-reactivity with other flaviviruses [130]. The PCR assay is useful in the first phase of illness, but only rarely successful in the second phase of disease [134]. In established cases of meningoencephalitis, analysis of CSF usually reveals a normal glucose and lactate level, a moderately raised protein level (CSF/serum albumin ratio), and pleocytosis [133]. At least two weeks after the first lumbar puncture, all patients showed a synthesis of TBEV-specific IgG- and/or IgM-antibodies in the CSF [130].

Regarding treatment, no specific therapy for TBE is known. Electrolyte balance, sufficient caloric intake, administration of analgesics and antipyretics, and if necessary, anticonvulsive agents constitute the most important targets in the clinical management of patients [130].

3.3.2. Hemorrhagic fever virus and tick-borne coltivirus

Aside of TBEV, hemorrhagic fever viruses (HFVs) and tick-borne coltivirus (TBC) present tick-borne transmission [135]. HFVs belong to either *Flavivirus* or *Bunyavirus* genera, which are distributed throughout Eastern Europe, Africa and Asia. Clinical picture is characterized by a biphasic disease that presents with febrile flu-like symptoms and hepatomegaly with hemorrhagic manifestations [136]. On the other hand, TBC causes a two or three-phase disease that resemble mild cases of RMSF without exanthema. Leukopenia and thrombocytopenia are frequently observed. Complications are rare, but may consist of meningoencephalitis, orchitis, hemorrhagic fever, pericarditis, and myocarditis [137]. Association with autoimmune phenomena has not been reported.

4. Tick borne diseases and autoimmunity

4.1. Tick-borne diseases and ADs

As a unique human model, LD has been extensively evaluated as one of the prototypes of the relationship between infection and AD [10]. LD must be considered as a differential diagnosis of ADs, especially when cutaneous, musculoskeletal, cardiovascular or nervous system compromise are present [138]. Further, as was previously described (see above), AD should be rule-out in all the cases where a TBD is suspected. Epidemiological setting and an accurate diagnostic approach (i.e., clinical history, physical exam and laboratory tests) are necessary to confirm the diagnosis.

4.2. Systemic sclerosis

A case report of a 61-year-old woman with Raynaud's phenomenon, nail-fold changes, circulating anti-centromere antibodies and skin thickening, mimicking SSc, was the first case reported suggesting an association between SSc and *B. burgdorferi* infection. The patient was positive for *B. burgdorferi* antibodies and the disease remitted after antibiotic treatment [139]. An additional case of Shulman syndrome triggered by *B. burgdorferi* has been described [140]. However, in a case-control study with 74 patients with SSc, there were no differences in seroprevalence of *B. burgdorferi* between patients and controls [141].

4.3. Sarcoidosis

B. burgdorferi and *Rickettsia* spp. infection were proposed as a cause of sarcoidosis [142,143]. Further, 46 Japanese patients with confirmed sarcoidosis and 150 controls were studied for *B. japonica, B. garinii* and *B. afzelii* [144]. Fifteen patients with sarcoidosis (32.6%) tested positive for *Borrelia* spp. as compared with two healthy controls (2.0%) ($p < 0.05$) [144]. However, in a recent meta-analysis [145], no association was found between sarcoidosis and *B. burgdorferi* or *Rickettsia* spp. infection. Nonetheless, a relation with mycobacteria and *P. acnes* was observed, which prompted authors to hypothesize that sarcoidosis etiology may be environmentally influenced as different microorganisms may be involved [145].

4.4. Dermatomyositis

Several case reports have suggested the relationship between dermatomyositis and *B. burgdorferi* infection. In these cases, patients developed proximal weakness, dysphagia, peripheral paresis and abnormal electromyographic findings [146,147]. Other patients developed a worse presentation, including fatal interstitial pulmonary fibrosis [148]. Thus, authors hypothesized that some cases of dermatomyositis could be triggered by *B. burgdorferi*.

4.5. Rheumatoid arthritis

Although chronic arthritis following LD is common, it is unclear whether *B. burgdorferi* infection may produce RA. LD arthritis may produce synovitis and bone erosion through molecular mimicry, which have increased the suspicion of *B. burgdorferi* infection as a triggering factor for RA. It has been shown that *B. burgdorferi* can induce in a few patients moderate to high titers of anti-citrullinated protein antibodies and rheumatoid factor in patients who are in the late disseminated phase [149–151]. In a cohort of 30 patients with

LD, 15 developed RA after a median period of 4 months [6]. LD should be considered as a differential diagnosis and a possible triggering factor for RA (including seronegative RA) in endemic areas. Further, De Boever et al. [152] reported a patient with seropositive RA and *C. burnetti* infection, who disclosed positive anti-liver kidney microsome-1 autoantibodies, accompanied by circulating immune complexes, which turned negative after treatment.

4.6. Ankylosing spondylitis

High levels of antibodies against *B. burgdorferi* have been reported to be more frequent in ankylosing spondylitis (AS) patients than in controls [153]. In contrast, in a cross-sectional study, 125 patients with AS did not disclose high levels of *B. burgdorferi* antibodies in comparison with controls, and there was no difference between HLA-B27+ and B27- patients [154]. Interestingly, in a cohort of 30 patients with chronic LD, only 2 developed AS [6]. Further, in a study aimed at determining the relationship between seropositivity to *Borrelia* spp. and *Ehrlichia* spp. in patients with spondyloarthritis, chronic low back pain and healthy subjects, antibodies were more frequent in patients than in controls, although no relationship was found with spondyloarthritis [155].

4.7. Polymyalgia rheumatica

Some reports have suggest that *B. burgdorferi* infection elicits polymyalgia rheumatica (PMR) [156,157]. In a German cohort of 19 patients with PMR and giant cell arteritis (GCA), 63% of patients disclosed a positive serology for *B. burgdorferi* [157]. Since a clear etiology of PMR has not been defined, *B. burgdorferi* may be considered as a possible trigger.

A single case reported by Chaumetin et al. [158], suggested the association of *Rickettsia* spp. and PMR. Patient was positive for anti-cardiolipin (aCL) antibodies and lupus anticoagulant (LAC); temporal artery biopsy was negative. Causal effect is unclear due to the late-onset of PMR (i.e., 2 months after rickettsial disease) and the persistence of autoantibodies after a year, which suggested a previous immunological abnormality.

4.8. Reactive arthritis

Rickettsioses usually generate myalgia and arthralgia. However, arthritis is seldom observed [159] and may be considered as a reactive arthritis. At least 13 reports of tick-borne rickettsoses and reactive arthritis [68,69,160–170], including 15 patients, are available in the literature, mainly associated with *R. rickettsi* and *R. conorii*. In one case rheumatoid factor was reported [161]. Both small and large joints may be involved, and oligoarticular compromise is often described. One patient disclosing concomitant erythema nodosum was been reported, as well as 3 similar cases associated with *Orientia tsutsugamushi* (i.e., a mite-borne rickettsiosis) [171]. An immune-complex mediated etiology was proposed by Aragon et al. [68], based on the presence of immune complexes and low complement levels. Further, some authors proposed that a specific peptide (i.e., 175-kDa) present in the Israeli type of Rickettsia could be arthritogenic [69].

4.9. Vasculitides

Previous reports suggested the relationship between *Borrelia* spp. infection and vasculitis. *Borrelia* spp. induces immune infiltration in vascular lining with intimal injury [172]. Some LD patients developed GCA symptoms with temporal artery biopsies disclosing classical findings [172]. Further, *B. burgdorferi* could be a trigger for GCA in endemic areas [173–175]. Likewise, a single case report of granulomatosis with polyangiitis (GPA) associated with *B. burgdorferi* infection is available. The authors reported otosinusitis, mononeuritis multiplex, and positive anti-neutrophil cytoplasmic antibody (ANCA), accompanied by a positive serology to *B. burgdorferi* [176], which suggested an association between GPA onset and *B. burgdorferi* infection.

Borrellia spp. infections have been proposed to play a role in Behçet's Disease (BD) etiology [177]. However, two case-control studies did not find any association between BD and *B. burgdorferi* infection [178,179].

The most frequently reported vasculitides associated with *Rickettsia* spp. affected the skin and were described as leukocytoclastic vasculitis [180–183]. Only one patient presented severe disease [180], and another disclosed positive antiphospholipid antibodies (aPL) [183]. Two cases of ANCA-associated vasculitides have been published [184,185]. Nigwekar et al. [186] reported a Henoch-Schönlein purpura (i.e., IgA vasculitis) in an eight-year old female, who presented with the classic triad, namely 1) arthralgia, 2) palpable purpura and 3) abdominal pain. However, we consider these symptoms may be due to rickettsial disease itself, thus vasculitis is unclear. A single report of a possible GCA triggered by *Rickettsia* spp. exists [187]. Interestingly, two independent groups [188,189] found no association between rickettsioses and Kawasaki disease.

Data regarding rickettsial disease and thromboangiitis obliterans (TA) are inconclusive. A recent Iranian case report [190] ascertained the identification of *Rickettsia* spp. in biopsy samples of a patient with TA and suggested to search for this microorganism in this entity. Further, the author portrayed possible mechanisms that may support this association [191]. This hypothesis was suggested by Bartolo et al. [192,193] in the 1980's, as seropositivity to several rickettsial species in TA patients was observed. Nevertheless, most of the results were positive for non-tick-borne rickettsioses (i.e., *R. prowazekii, R. typhus*) or bacteria previously considered to be *Rickettsiae* (*C. burnetti*). Thus, there is no support for a causal relationship between *Rickettsia* spp. and TA.

A restrospective study searched for ehrlichial involvement in primary vasculitides. The authors reported a positive serology to *Ehrlichia* spp. in 3 (5.5%) patients, who presented with either polyarteritis nodosa, unspecified vasculitis or allergic purpura [194]. In contrast, a Greek study found no association between *A. phagocytophila* and Kawasaki disease [188]. Although a case was reported to be associated with *Anaplasma spp.* in Cyprus, no causal relation could be ascertained [195].

Association between Kawasaki disease and *C. burnetii* has been discussed. A case report argued the possible association between these two entities [196]. Nevertheless, a cross-sectional study in children disclosed only one case of simultaneously presentation of Kawasaki disease and *C. burnetti* infection. Lack of controls precluded any conclusion [188]. Interestingly, three cases of essential and mixed cryoglobulinemia associated with Q fever have been reported [197–199]. Association between Q fever and production of ANCAs has been reported, despite the absence of overt vasculitis [200,201]. Further, cases of GCA and Takayasu arteritis associated with *C. burnetti* infection have been documented [202,203]. Finally, a single case of endocarditis and leukocytoclastic vasculitis after Q fever onset was reported [204]. No immune mechanism has been proposed to explain these associations, although an intense immunologic response may responsible [202,203].

4.10. Uveitis

Uveitis secondary to *C. burnetii* infection has been described. Rossiter-Thorton et al. proposed that it might be either due to a

direct effect of the microorganism or, more likely, due to a delayed T-cell hypersensitivity response in association with HLA-B27 [205]. Interestingly, some data support that uveitis may not result from direct injury to the ocular structure by *C. burnetii* but rather from inflammatory injury [206,207]. Intraocular infection with *C. burnetii* appears unlikely [208].

4.11. Multiple sclerosis

Similarities between neuro-borreliosis and MS suggest that *B. burgdorferi* infection could trigger MS [209,210]. A case report showed a positive serology to *B. burgdorferi* in a newly-diagnosed patient with MS [211]. *B. burgdorferi* infection was observed during some MS exacerbations and was associated with a failure of immunomodulatory treatment [212]. A cross-sectional study in 769 patients showed a statistically significant relationship between MS and positive serology to *Borrelia* spp. [210]. However, a study including 44 MS patients did not report differences when compared with controls [213].

Rickettsioses have also been associated with MS. The first direct association was proposed by Pierre Le Gac, back in the 1960's, when he claimed an infectious etiology for MS; *Rickettsia* spp. were to be blamed for this phenomenon and antibiotic treatment appeared to improve symptoms [214]. These results appeared to be reproduced by Jadin et al. [215]. Findings were based mainly on a more frequent positive serology to *Rickettsia* spp. in MS patients compared with controls, which was further reproduced [216]. In contrast, some other authors found no relationship [216–218]. Interestingly, two bacteria were alleged the most frequently associated to MS: *Chlamydia pneumoniae* and *C. burnetti,* which were previously considered *Rickettsiae*. Novel methods showed that they belong to a different group. No tick-borne rickettsioses have been involved. Although some authors still hypothesize this connection [219,220], more recent evidence do not support the involvement of *Chalmydiae*, *Coxiella* or *Rickettsiae* in the pathophysiology of MS, nor antibiotic therapy utility [221–223].

4.12. Guillain-Barré syndrome

GBS is usually triggered by infectious diseases through molecular mimicry, resulting in autoantibodies production [224,225]. Interestingly, a case report presented a patient with *Borrelia* spp. infection who developed GBS symptoms, with a demyelinating pattern, which improved after plasmapheresis [7]. Other cases have supported this observation [226–228]. In a study involving 36 patients with infection by *B. afzelii*, eleven disclosed positive autoantibodies against myelin basic protein, which were more frequent in young women [229]. *Campylobacter jejuni* and *Borrelia* spp. infections may share similar mechanisms of GBS-associated autoantibody production. Nonetheless, other infections have been associated with GBS. At least five case reports [230–234] involving tick-borne rickettsoses (*R. rickettsii, R. conori* and *R. helvetica*), reported GBS [230–233] or chronic inflammatory demyelinating polyneuropathy [234]. A case report, presented as a conference poster, disclosed an association with GBS, in which a positive molecular test (i.e., PCR) for *E. chafeensis* was obtained from cerebrospinal fluid [235]. A case report of patient with GBS and Q fever was described, who disclosed a sensorimotor polyradiculoneuropathy pattern in electromyography that improved after antibiotic therapy [236]. Some authors suggest that patients with polyradiculoneuropathies, fever, headache and neuro-ophthalmologic disorders should be tested for *C. burnetii* [237]. On the other hand, four cases of GBS and tularemia have been reported, including ulcero-glandular and typhoidal subsets, although none was associated with tick bites [238–240].

4.13. Transverse myelitis

Recently, TM has been reported as a common presentation of neuro-borreliosis, during the early disseminated phase of LD [241–246], although the pathogenesis is unknown. Acute inflammation, apoptosis and autoimmune processes have been proposed as possible mechanisms [52]. Oleson et al. [245] identified a case of TM in which co-infection by *B. burgdorferi* and *B. microti* was documented. Although the autoimmune component of TM is uncertain, its association with other ADs is clear [247]. In addition, a case of TM associated with rickettsial disease was reported, although autoimmune etiology was not confirmed [248]. A case report described a patient with serological evidence of *C. burnetii* and progressive sensory-motor dysfunction of the limbs, suggesting TM. The authors concluded that direct infectious or para-infectious pathogenic mechanisms could have been related [249]. *C. burnetii* should be considered among infectious agents causing TM.

Given the viral tropism for the CNS, TBEV can cause ADs, such as demyelinating disorders (i.e., MS) or acute disseminated encephalomyelitis (ADEM). Concerning MS, viruses have been implicated in the emergence of the disease, through a variety of mechanisms, such as molecular mimicry, bystander activation and epitope spreading [250]. Although association among MS and TBEV is not confirmed, a single case with both entities was reported [251]. On the other hand, a causal relation between ADEM and TBEV is unknown. However, it is important to consider Powassan virus infection among the differential diagnosis of patients presenting with encephalitis [252].

4.14. Autoimmune thyroid disease

A patient with lichen sclerosus and autoimmune thyroiditis following infection by *B. burgdorferi* led to hypothesize that *B. burgdorferi* could trigger thyroid autoimmunity [253]. An *in silico* study demonstrated that *B. burgdorferi* share homology with thyroglobulin, thyroid peroxidase and thyroid-stimulating hormone (TSH) receptor, the most common targets of autoantibodies in AITD, suggesting molecular mimicry. Interestingly, binding motifs for several MHC-II were found to be associated with these epitopes [254,255]. Nevertheless, in a population-based study, *B. burgdorferi* IgG antibodies were not associated with autoimmune thyroid disease (AITD) [256]. The interaction of environmental exposures, genetic background and infections (i.e., autoimmune ecology) could join to trigger thyroid autoimmunity [257,258]. Thus, in susceptible individuals, *B. burgdorferi* could elicit AITD.

Further, a single case of GD and *Rickettsia* spp. was reported by Marangou et al. [67]. Interestingly, the authors offer a compelling hypothesis for molecular mimicry in this entity. They demonstrated the homology between rickettsial proteins and TSH receptor. Further, they ascertained that these homologous segments presented binding motifs for HLA-DRB1*0301. In addition, Levy et al. [259] found a rather high frequency of anti-thyroid autoantibodies, antinuclear antibodies (ANAs), rheumatoid factor, circulating immune-complexes, and anti-platelet autoantibodies during Q fever.

4.15. Autoimmune hemolytic anemia

Babesiosis frequently presents clinical hemolysis, which may portray an autoimmune characteristic. Three case reports, including eleven asplenic patients with babesiosis and AHA have been described. All of them disclosed positivity on direct antiglobulin tests; two of them received plasmapheresis with positive outcomes. Interestingly, one non-splenectomized patient disclosed

similar features [103–105]. Shatzel et al. described two patients with history of Evan's syndrome requiring splenectomy due to AHA, who achieved remission. Both of them presented a relapse after babesia infection [106]. Recently, six cases of asplenic patients without history of autoimmunity, developed warm AHA after *B. microti* infection, despite antimicrobial treatment and resolution of parasitemia [11]. Plausible mechanisms for post-babesiosis AHA in asplenic patients are immune-complexes formation or Type-III hypersensitivity [11]. These immune complexes are removed inefficiently by macrophages in asplenic patients and may activate the classical complement pathway with an intense release of inflammatory mediators and subsequent lysis of red blood cells [11].

Levy et al. [259] reported for the first time AHA associated with *C. burnetti* infection, followed by De Boever et al. [152], who described a possible case of AHA (i.e., anemia and irregular agglutinins), but no Coombs test was described. In contrast, in a case report with acute Q fever together with AHA and tubulointerstitial nephritis [260], authors hypothesized that autoimmune mechanisms could have driven the hemolysis since direct Coombs test was positive. However, they stated that the lack of agglutinin test in their laboratory hindered any conclusion about a differential diagnosis of the cause of AHA [260].

4.16. Immune thrombocytopenia

Association between *Babesia* spp. infection and IT has been described. Nevertheless, mechanisms of IT associated with babesiosis remain elusive and require further characterization [107]. On the other hand, Levy et al. [259] reported the first case related to Q fever, which was replicated by De Boever et al. [152], who reported a case of IT (i.e., anti-platelet autoantibodies and thrombocytopenia).

4.17. Antiphospholipid autoantibodies and antiphospholipid syndrome

High levels of aPL in LD patients have been reported [261]. In a cross-sectional study, 106 patients with LD were tested for aCL, anti-beta-2- glycoprotein-1 antibodies (anti-β2GP1) and LAC. Eighty percent of patients disclosed positive aCL or anti-B2GP1 autoantibodies, with an IgM isotype predominance. However, lack of healthy controls hindered a statistical association [262]. Interestingly, a case report described a patient with high aCL, anti-β2GP1 IgM titers and positive LAC with pulmonary thromboembolism during LD and *Plasmodium falciparum* infection, suggesting antiphospholipid syndrome (APS) [263]. Thus, it is tempting to speculate that aPL could be produced during LD.

Three cases reported the detection of aPL, involving both *R. conorii* and *R. rickettsii* infections [66,158,183]. Interestingly, Walker et al. [66] proposed the endothelial tropism of *Rickettsia* spp. as a potential mechanism. ECs are destroyed and aPL may appear given self-antigen release; further, they found anti-endothelial antibodies. Seventy-one percent of patients disclosed either aCL or anti-phosphatidyl serine autoantibodies, whereas 50% presented anti-endothelial antibodies. These autoantibodies were proposed to be related with coagulation abnormalities and vascular changes.

Infections are known to induce aPL [264] and several case reports have described its presence during *C. burnetti* infection [152,265–269]. Prevalence of aPL in Q fever ranges from 42% to 76%, and a 44% (CI 95%, 2.8–702.5) risk ratio of developing aPL after infection has been reported [270,271]. Interestingly, patients with Q fever and IgG aCL positivity disclose a higher risk for thrombotic events [272]. However, case reports of overt APS are scarce. A case of a patient with renal thrombosis, Q fever and aPL is available [273], as well as a case of splenic infarction [274]. Valvular vegetations in patients with Q fever might be an expression of APS [275]. Limited evidence for overt APS in *C. burnetti* infection in the literature should not imply a low risk in patients with Q fever [272].

4.18. Autoimmune liver disease

A case report on a patient with primary biliary sclerosis (PBS) described a temporal association with *B. burgdorferi*, which prompted the authors to speculate that molecular mimicry between *B. burgdorferi* and disease-specific mitochondrial antigens may account for the breakdown of self-tolerance and the induction of anti-mitochondrial autoimmunity [276]. Interestingly, Bogdanos et al. [277] provided *in silico* evidence of molecular mimicry between the major mitochondrial autoantigen in PBS and *B. burgdorferi* flagellin. However these data are epiphenomena and not likely to have any clinical basis.

A possible relation between autoimmune hepatitis (AIH)/PBS overlap syndrome and Q fever has been proposed. Levy et al. [259] reported that 23% of patients affected by Q fever developed anti-smooth-muscle antibodies (ASMA), and found a rather high frequency of anti-mitochondrial antibodies (AMA). Two cases of AIH have been described, who displayed several positive autoantibodies (i.e., ASMA, AMA, ANCA, ANAs, etc.) [278]. Further, a description of a patient with both diseases and serological evidence of positive ANAs, ASMA, AMA, and anti-M2 antibody titer was obtained [279]. The authors suggested that *C. burnetii* might trigger autoimmune liver disease through molecular mimicry, as the β-subunit of bacterial RNA polymerase (i.e., a non-species-specific bacterial protein) was shown to be an autoantibody target in PBS [280]. Additionally, a case of Q fever in an elderly woman reported positive ANAs, aCL, ASMA and anti-cytosol antibodies. She disclosed altered hepatic profiles, which may suggest an autoimmune liver disease, although liver biopsy was consistent with Q fever [281].

5. Tick borne diseases and likely associations with autoimmunity

5.1. Systemic lupus erythematosus-like syndrome

A patient with psoriasis, who was found to have *B. burgdorferi* antibodies, developed, systemic lupus erythematosus (SLE)-like syndrome after the beginning of infliximab treatment. Authors hypothesized that TNF-α blockade could have eased infection by *B. burgdorferi* which expressed as SLE-like syndrome [282]. However, as authors stated, we consider infliximab might be the main responsible of this association.

5.2. Fibromyalgia

It has been suggested that *B. burgdorferi* may trigger fibromyalgia [283]. The association between fibromyalgia and LD in endemic areas have led to ascertain that fibromyalgia is a potentially treatable and curable disease, and it should be recognized as a LD sequelae [284]. However, antibiotic treatment does not seem to be effective [285]. Case reports do not reflect causation and data from case reports may correspond to coincidental phenomenon or epiphenomena.

5.3. Morphea

Morphea, also known as localized scleroderma, is a disorder characterized by excessive collagen deposition leading to thickening of the dermis, subcutaneous tissues, or both. Clinical differentiation from SSc is mandatory. *B. burgdorferi* has been proposed

as a triggering factor. Some studies have shown the presence of *B. burgdorferi* in sclerotic lesions from patients with morphea [286,287]. Other reports have demonstrated a higher seroprevalence of antibodies against *B. burgdorferi* as compared with controls [288,289]. Some authors have hypothesized that morphea could be caused by specific *B. burgdorferi* subspecies, which are more prevalent in Europe and Asia than in USA. However, contradictory evidence exists regarding *B. burgdorferi* as an etiological factor [290–297].

5.4. Crohn's disease

A case report of a patient with Crohn's disease was reported [197]. Interestingly, an increased flare number associated with *C. burnetti* infection in Crohn's disease has been described [298].

5.5. Addison's disease associated with celiac autoantibodies

A case report [299] showed a male child who presented to the emergency room as an aseptic meningitis. Serology presented positive IgG for *E. chafeensis* and *Anaplasma* spp. However, one month later, Addison's disease was diagnosed and positive celiac autoantibodies (i.e., tissue transglutaminase A, endomysial) were obtained. The authors considered *Ehrlichia* spp. and *Anaplasma* spp. infection triggered autoimmunity.

5.6. Protein S deficiency

Recently, a case report described a 38-year-old man with acute Q fever associated with positive IgM anti-PS antibodies, and IgM and IgG aCL antibodies. The patient presented pulmonary embolism (PE) –like symptoms that elicited treatment with unfractioned heparin, which was later ruled out by a chest angioscan. Noteworthy, D-dimers were moderately elevated. Thrombophilia screening was performed and revealed numerous thrombophilic factors including a 1) severe deficiency in protein S associated with highly positive IgM anti-PS antibodies, 2) a moderate deficiency in protein C, 3) a heterozygous factor V Leiden mutation, and 4) positive IgM and IgG aCL antibodies. Of note, PS activity was recovered as IgM anti-PS antibodies decreased. The authors considered a PE could have been abrogated as early anticoagulation was started [300].

This case report prompts discussion on the uncertain value of anti-PS antibodies in thrombotic risk assessment. First, we must consider that acquired PS deficiency due to anti-PS antibodies usually discloses both reduced PS activity and PS antigen [301]. The latter was within the normal range in this case report. Second, some authors stress the possibility of misdiagnosis of PS deficiency based solely on low PS activity and propose the measurement of free PS antigen as a surrogate of PS activity [302], which was unaltered in this patient. Third, as IgM isotype antiphospholipid antibodies (e.g., aCL, anti-β2GP-1) appear of low predictability in antiphospholipid syndrome [303,304], IgM anti-PS antibodies may present a similar low value. Nonetheless, some authors have reported up to a 7-fold increased risk of prospective thrombosis associated with IgM anti-PS antibodies in patients with antiphospholipid antibodies, even when adjusted by other thrombotic risk factors (e.g., age, sex, lupus anticoagulant positivity, antiphospholipid antibodies); this phenomenon was not observed with IgG anti-PS autoantibodies [305,306]. Thus, IgM anti-PS antibodies deserve further research. In any case, we highlight the presence of autoimmune phenomena related to Q fever: IgM anti-PS antibodies, and positive IgM and IgG aCL antibodies.

5.7. Other autoimmune diseases

A case described a 34-year-old asplenic woman, who developed focal ocular vasculitis, accompanied by positive rheumatoid factor, ANAs, decreased serum C3 complement, and systemic involvement (i.e., including the kidneys, joints, pericardium, and small vessels). Intraerythrocytic *Babesia* spp. were observed and positive serology to *B. microtii* was obtained. Clinical picture was thought to be secondary to immune-complex deposition caused by *Babesia* spp. chronic infection. Although immune-complexes were not identified, the severe course provided circumstantial evidence for immune complex disease [307].

Further, a Spanish report was found, in which adult onset Still's disease appeared to be triggered by a rickettsial infection. However, we could not retrieve this paper [308]. Additionally, a case of optic neuritis was described, even though no anti-aquaporin autoantibodies were measured [309] and a probable case of myasthenia gravis associated to *R. helvetica* was informed, but no autoimmune etiology was confirmed, although no other causes were identified [310].

6. Tick borne diseases prevention

A number of measures for prevention and control of TBDs have been proposed, including vaccination, prophylaxis, personal measures for protection and environmental measures. In the 1990s, a vaccine for LD was introduced. However, it was withdrawn due to slow acceptance owing its high cost and alleged arthritogenic effects, despite adequate immunogenicity [311]. Vaccination is more often found in Europe and Asia due to a high burden of tick-borne viral encephalitis [24,312] and it should be offered to at-risk travelers (e.g., hiking or camping in forested areas up to an altitude of 1500 meters) to rural endemic areas during the period of transmission (i.e., April to November) [313]. Research on new vaccines is underway [314].

In terms of prophylaxis of TBDs, prophylactic antibiotics when an alleged tick bite is accompanied by erythema migrans have been recommended. A randomized clinical trial demonstrated 87% reduction of LD with single 200 mg dose of doxycycline, within 72 h of a tick bite by *I. scapularis* [315]. Further, as TBDs may be transmitted by blood products, the clinician is advised to use leukocyte-reduced blood, particularly in highly endemic areas [24].

Regarding personal protection measures, adequate clothes are essential. Whenever an individual will be exposed to tick-infested areas, it is advised to wear boots, long pants, long-sleeve shirts, and light colors that allow tick identification. Tucking pants legs into the top of the socks and placing a ring of masking tape are advised. Avoiding highly tick-infested areas and leaf litter reduces exposure. When hiking is undergone, sitting on downed logs must be avoided, as they may be full of nymphs. Topic repelents containing N,N-Diethyl-meta-toluamide (DEET), with formulas between 20% and 50%, are advised. Applying permethrin on clothes is useful, and may confer protection for up to a month, even after several washings; topic application must be avoided [1,24,316,317]. Due to increasing tick resistance to insecticides and environmental concerns, 'ecofriendly' options are under study [318,319]. Frequent self-inspection to spot ticks must be implemented, as some TBDs may be transmitted within an hour. As ticks may be transported on clothes from the infested area, it is advised to change clothing and placing it in plastic bags, prior to enter into a vehicle. Permethrin may be applied to livestock to reduce tick population. Washing clothes in hot water and drying on high heat kill ticks and prevent residence invasion. Bathing within 2 h of tick exposure prevents attachment of ticks. A light permethrin spray around bedding is useful to hinder tick bites during the night [1,24,316,317].

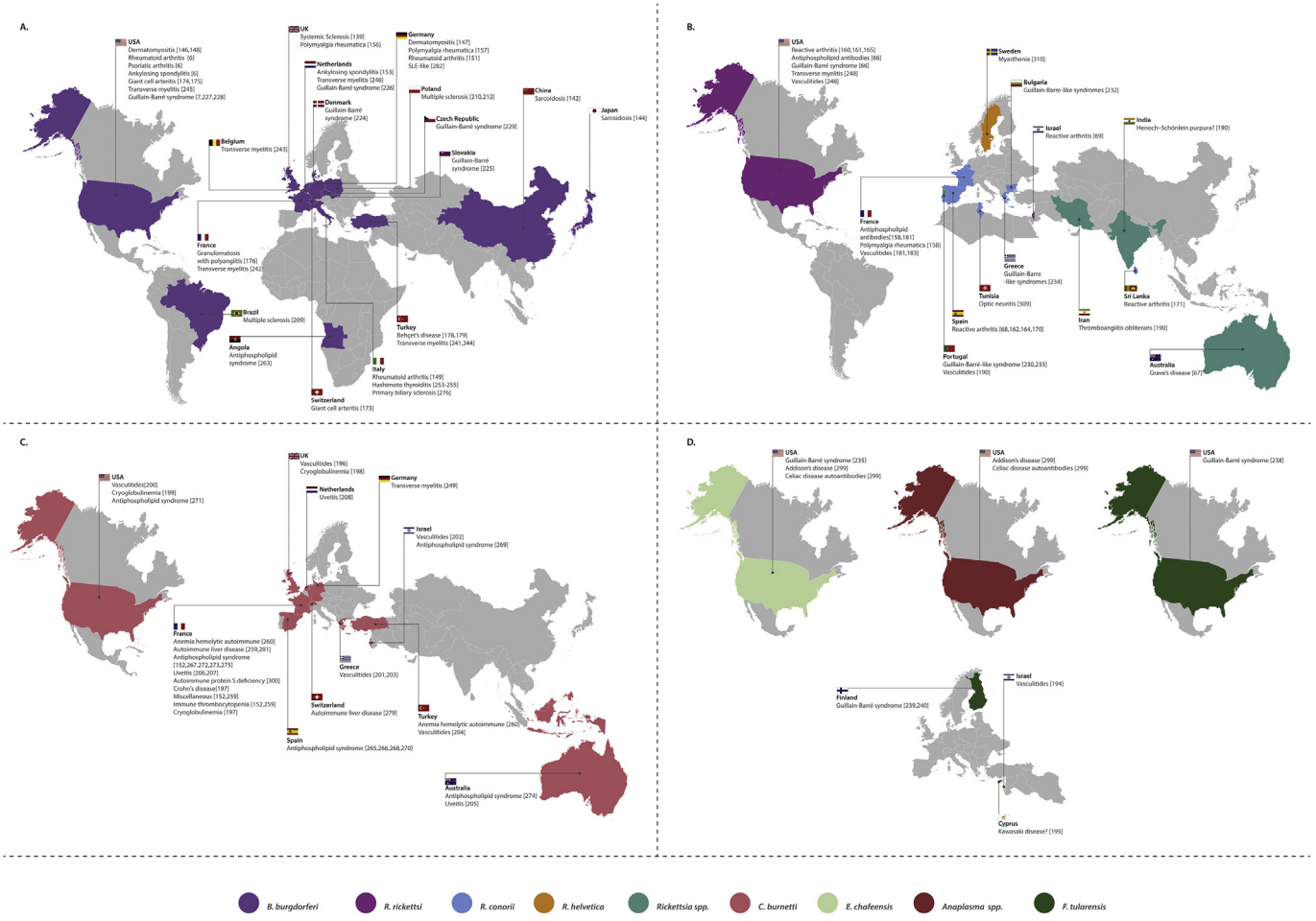

Fig. 1. Geographical distribution of autoimmune diseases related to bacterial infections transmitted by ticks. A. Borreliosis, B. Rickettsioses, C. Q Fever, D. Ehrlichioses, Anaplasmosis and Tularemia.

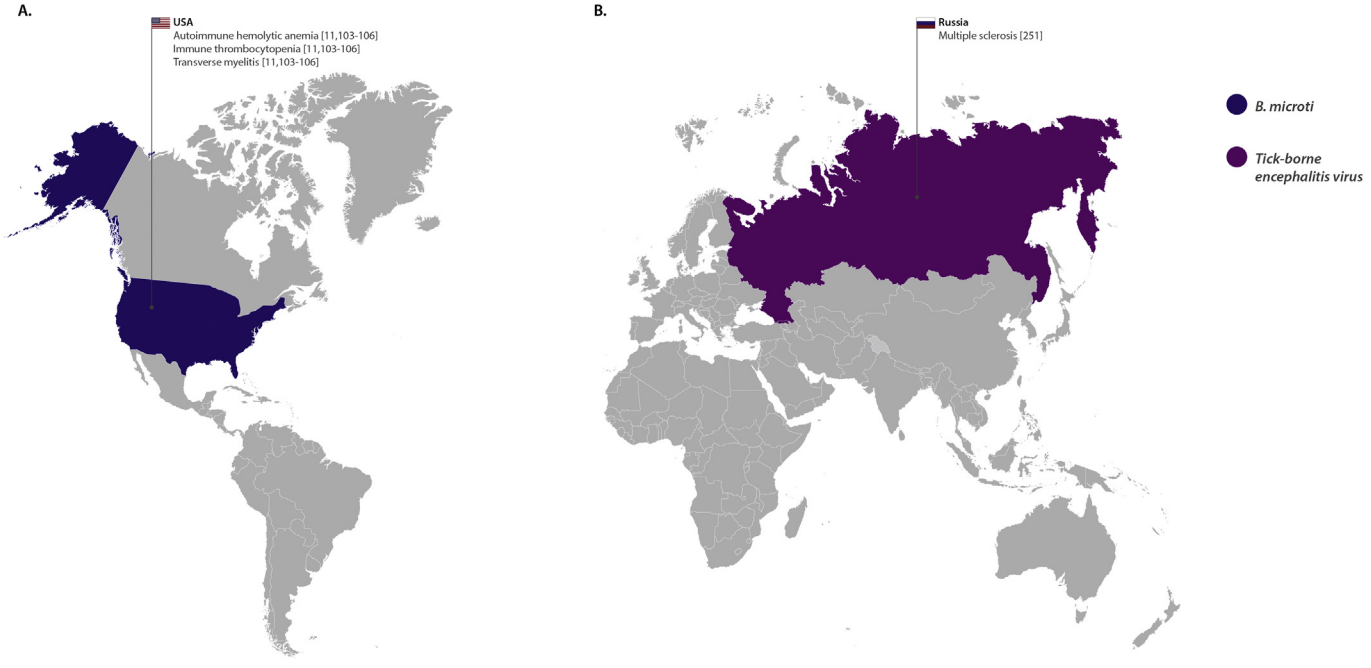

Fig. 2. Geographical distribution of autoimmune diseases related to parasitic and viral infections transmitted by ticks. A. Babesiosis, B. Tick-borne encephalitis virus.

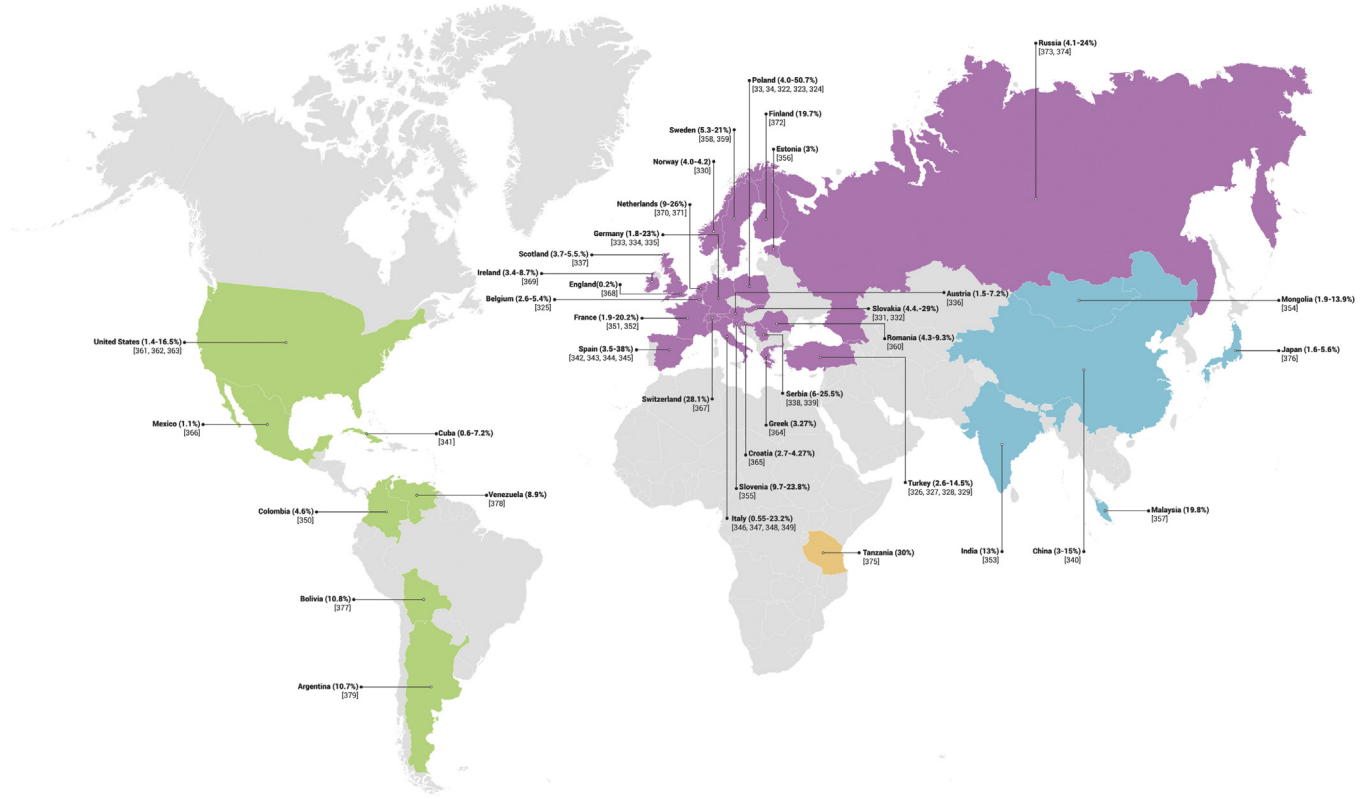

Fig. 3. Worldwide seroprevalence of *B. burgdorferi* in healthy and population at risk. Differences in seroprevalence could be secondary to weather, landscape and seasons.

Modifications of home environment, such as spraying pesticides around the house or modifying landscape, are not clear to reduce transmission [1].

Pets are prone to tick infestation and, consequently, to TBDs in endemic areas. Previous recommendations are applicable and tick removal must be done as explained; little progress on vaccination strategies for pets has been achieved, in spite of its growing importance [320,321].

If a tick is observed to be attached to the skin, it must be removed as soon as possible, ideally within the first 36 h. Its removal must be always using fine-tipped forceps (e.g., tweezers), grasping the tick close to the surface of the skin and removing it with a constant and steady motion. Removal with bare or gloved hands must be avoided, as crushing the tick may release infectious agents that may cross dermis barrier or yield infectious aerosols. Afterwards, the area must be cleaned with local antiseptic. Nevertheless, the area must be checked frequently to detect rash or signs of infections, and systemic infection surveillance should be implemented for at least 4 weeks. Noteworthy, most patients do not recall a tick bite, probably because a nymph is too small to be spotted. Unorthodox methods, such as burning the tick or applying either glue or fingernail polish are not recommended, as do not ease tick removal and, instead, may foster disease transmission. Although seldom seen, if larval ticks are noticed, a piece of tape applied to the skin or clothing easily removes them. Whenever a tick is removed, its preservation will help the clinician. Placing it into isopropyl alcohol or between two clear tape pieces are useful methods [1,24,316,317].

7. Conclusion

Climate change and landscape modifications by humans have favored ticks spreading and have increased the incidence of TBDs. The clinician should consider TBDs among the differential diagnoses of autoimmune-like conditions in areas of tick infestation (Figs. 1–3) [33,34,322–379]. Epidemiological setting and an accurate diagnostic approach are necessary to confirm TBDs. Prevention strategies, including education on TBDs, should be promptly implemented to control burden of disease and the potential escalation of ADs incidence triggered by tick-transmitted infections. In addition, further studies are warranted to clarify the role of TBDs and autoimmunity.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jaut.2017.11.007.

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